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In Reply to Mansha

To the Editor: We thank Dr. Mansha for the kind words and interest in our recent study (1, 2). We agree that human papillomavirus (HPV) status does predict for disease outcome, even in the reirradiation setting, as demonstrated by Davis et al (3). These are challenging analyses to do given the differences in recurrence patterns in patients who are HPV positive, in terms of location, time to recurrence, and the changing epidemiology of HPV positivity. In our study, p16 status was used as a surrogate for HPV positivity. p16 protein status was available for 27 of the 173 head and neck squamous cell cancer patients and did not significantly influence survival or tumor control, as demonstrated in Supplementary Figure 1 and Supplementary Table S2 in our article (1).

Patients with an initial diagnosis of nasopharyngeal carcinoma overall constituted a minority of patients in the dataset. As Dr. Mansha alluded, tumor outcomes among nasopharyngeal carcinoma patients were notably better than in those with tumors involving other head and neck subsites, with 2-year locoregional control and progression-free survival rates of 86% and 73%, respectively. This is consistent with prior reports (4-7). Of the 16 patients with initial nasopharyngeal presentation, 3 presented with intracranial extension (T4) disease.

Last, in regard to relevant organ-at-risk doses, we believe detailed volumetric analyses are required for this information to be useful. These investigations are the subject of future research. Previous publications from other institutions have addressed maximum point doses, although the clinical applicability of this information remains less clear (8, 9). Although we have attempted to present a thorough and coherent analysis of our data using intensity modulated radiation therapy for head and neck reirradiation, there are clearly many questions that remain to be explored in future studies.

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"Freezing" the Tumor in a Known Position During Radiation Therapy

In Regard to Boda-Heggemann et al

To the Editor: It was always hoped that if patients held their breath, tumors would stay still. The introduction of multiple short (roughly 20-second) breath-holds in air, to reduce the movement of target organs, is improving radiation therapy delivery for breast cancer (1) and ought to improve the delivery for other thoracic and abdominal tumors. It is important, however, to be aware that tumors do not stay completely still during breath-holding (2-4). First, there is settlement of

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the chest, diaphragm, and abdominal organs when the breath-hold is first established (3, 5, 6). Second, there is shrinkage of the chest volume throughout breath-holding because oxygen continues to be extracted from alveolar gas and is not replaced by an equal volume of carbon dioxide (7). These physiological changes are in addition to the issues of reproducibility of organ position between each breath-hold.

Colleagues should also be aware that patients with cancer can already breath-hold for >10 times longer than in these multiple short breath-holds using air (1). Parkes et al (3) have just achieved single prolonged breath-holds for >5 minutes using a non-invasive mechanical ventilation technique with 60% oxygen. Here, the initial settlement movement over the first 10 to 15 seconds of the breath-hold was typically 3 mm, and in 15 patients the chest deflated by about 2 mm/min in the inferior-superior direction (the direction of largest motion in this study). Peguret et al (2) have achieved single "apnea-like breath-holds" for >11 minutes using a high-frequency percussive ventilation technique with 100% oxygen. Movements during their ventilation technique were measured with computed tomography and evaluated in detail in 2 patients, showing movement from the start to the end of the ventilation that was typically 2 to 4 mm and occasionally larger.

Whereas such prolonged breath-holding techniques have further clinical potential to optimize both imaging and delivery of x-ray and particle beam therapy in a single breath-hold, they also emphasize the urgent need for more research on the position changes of both tumors and healthy tissue throughout breath-holding.

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